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1. Your reference — LPB/P102231GB

2. Patent application number *(The Patent Office will fill in this part)* — 0308150.2 — 9 APR 2003

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

CXR Biosciences Limited
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Scotland, United Kingdom

Patents ADP number *(if you know it)* — 8606493001

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4. Title of the invention — Method of Determining Xenograft Responses

5. Name of your agent *(if you have one)* — Harrison Goddard Foote

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Belgrave Hall
Belgrave Street
Leeds
LS2 8DD

Patents ADP number *(if you know it)* — 14571001 — 7631310002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

yes

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Continuation sheets of this form	
Description	12
Claim(s)	6
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Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature: Harrison Goddard Foote — Date: 9 April 2003

12. Name and daytime telephone number of person to contact in the United Kingdom: Dr Lisa Brown — 0113 233 0100

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Method of Determining Xenograft Responses

The present invention relates to a method of genetically modifying or engineering cells or tissue and introducing said cells or tissue into a non-human animal, especially but not exclusively, as a xenograft. The genetic modification(s) made to the xenograft cells or tissue are such as to allow reporting of cell physiological processes within the cells implanted into the host animal, for the purpose, especially but not exclusively, of monitoring cell physiological processes within the xenograft and/or monitoring the effects of drugs or other therapeutic interventions on the xenograft. The present invention further includes products comprising genetically engineered cells and/or tissues comprising such genetically engineered cells and uses thereof.

Background to the Invention

Experimental xenografts in animals are an essential tool in cancer research and in studying the efficacy of anti-cancer drugs or other therapeutic procedures. Experimental xenografts also have potential applications more generally in the study of the mode of action of drugs or other chemical compounds or biological substances or agents in biological systems. For example, it is known from the prior art in US 6,107,540 and US 6,365,797 to use human prostate cell lines to generate a cancer xenograft in immuno-compromised SCID mice and to monitor disease progression and effects of therapeutics on the xenograft tumour. However, the information that can be gained from prior art experimental approaches is limited. This is due to the few informative parameters of xenograft physiology that can be measured sufficiently or effectively. In addition, there is the problem that the xenograft itself is only accessible by invasive or cumbersome methods, which typically necessitates culling of the animal. Accordingly, xenograft measurements may only be made at a limited number of specific time points. A yet further problem resides in quantitative assessment of xenograft cell proliferation status. Typically, measurement of xenograft size is used as the indicator however such measurements are prone to

inaccuracies and are not capable of picking up subtle changes that may occur in progression or regression of a xenograft tumour.

An improved method of determining the quantity and quality of information that can be generated from the introduction of a xenograft into a host, including the ability to detect the very earliest stages of a response, based on knowledge of the mechanisms involved, before the response would be evident using existing methods, would offer immediate advantage to the prior art. Such a method would not only benefit the understanding of physiological processes of xenografts in a host but would also provide an improvement to the determination of efficacy of candidate therapeutic agents in xenograft animal models and their effect on physiological processes.

Statement of the Invention

The present invention resides in the modification or engineering of cells that are intended for introduction into a host as a xenograft, the modification or engineering of the cells comprising inclusion of at least one suitable reporter system. Inclusion of a reporter system advantageously allows for the determination of xenograft parameters of interest through appropriate and convenient measurement systems. Accordingly, many of the problems associated with the prior art can be mitigated and the information from experimental xenografts can be expanded.

According to a first aspect of the invention there is provided a method of simulating progression of a xenograft in an animal model comprising:

(i) genetically modifying or engineering a cell so as to incorporate at least one reporter molecule and/or reporter gene into said cell either before or after implantation of said cell into an animal;

(ii) implanting said modified cell into said animal model and allowing a xenograft to grow for a sufficient period of time; and

(iii) measuring at least one parameter of a selected biochemical/ physiological response associated with the reporter molecule or reporter gene.

Preferably, there is a plurality of genetically modified or engineered cells and more preferably the cells are human or non-human in origin and may be in the form of a primary isolate derived from, for example a tumour or they may be in the form of an immortalised or established cell line.

Preferably, the modified cells that are implanted into the animal host are selected from the group comprising cells derived from a tumour for example and without limitation a liver, brain, gut, adrenal, kidney, skin or any other organ or tissue which it is desired to xenograft. The cells may be prepared directly from such tumours or they may be an established cell line, for example and without limitation a cell line selected from the list of tumour cell lines listed at http://dtp.ncl.nih.gov/branches/btb/tumor-catalog.pdf.

It will be appreciated that the xenograft cells of the present invention are not limited to tumour cells, they may be for example embryonic stem cells or they may be derived from any type of living cell of mammalian or non-mammalian origin. For example, bacterial cells that produce a suitable reporter response may be employed to detect certain parameters in the host animal.

The cells which have been transiently or stably modified or engineered so as to incorporate at least one reporter molecule or reporter gene into them will hereinafter be conveniently referred to as the "reporter cell/system".

Throughout the description and claims of this specification, the words "comprise" and "contain" and variations of the words, for example "comprising" and "comprised", mean "including but not limited to", and are not intended to (and do not) exclude other components, integers, moieties, additives or steps.

Reference herein to a "reporter molecule" is intended to include chemical moieties used for labelling a nucleic acid or amino acid sequence. They include, but are not limited to, radionuclides, enzymes, enzyme substrates, fluorescent, chemiluminescent or chromogenic agents. Reporter molecules associate with, establish the presence of, and may allow quantification of a particular nucleic or amino acid sequence.

Reference herein to "reporter genes" are intended to include nucleic acids and fragments thereof encoding a functional protein. The reporter genes referred to in the present invention can "report" many different properties and events, for example apart from normal physiological processes they can report the strength of promoters, whether native or modified for reverse genetics studies; the efficiency of gene delivery systems; the intracellular fate of a gene product, a result of protein traffic; interaction of two proteins in the two-hybrid system or of a protein and a nucleic acid in the one-hybrid system; the efficiency of translation initiation signals; the success of molecular cloning efforts; and effects of exogenous agents on physiological processes.

Reporter genes are nucleic acid sequences encoding directly or indirectly assayable proteins. They are used to replace other coding regions whose protein products are unsuitable or not amenable to the assay envisaged. Suitable reporter genes that are konown in the art and may be used in the method of the present invention are selected from those genes encoding proteins including but not limited to: chloramphenicol, acetyltransferase, β–galactosidase, β–glucuronidase, luciferase, beta-galactosidase, green fluorescent protein, secreted alkaline phosphatase (SEAP), major urinary protein (MUP) or human chorionic gonadotrophin (hCG). It will be understood that the above list of suitable reporter genes is not exhaustive or exclusive and is not intended to limit the scope of the application. The skilled artisan may select another reporter system which will equally be applicable to the method of the present invention.

It will be appreciated that reporter genes can be attached to other sequences so that only the reporter protein is made or so that the reporter protein is fused to another protein (fusion protein).

Reference herein to a "reporter agent" is intended to include a protease or kinase or protein or RNA or any other biochemical moiety that effects changes in cell protein or mRNA stabilisation.

Preferably, the animal model is a rodent and more preferably is a mouse or rat of wild type or of a specifically selected genetic background, for instance one in which drug metabolism characteristics are modified.

Preferably, the animal model may have more than one different population of reporter cells/system implanted therein.

The method of the present invention comprises using genetically engineered cells of human or non-human origin so as to become a reporter system by the incorporation of one or more reporter molecules or reporter genes or transgenes into the selected cells preferably in a manner permitting replication of the incorporated reporter genes with replication of the host cell genome. Preferably, the reporter molecule or transgene is suitable for the purpose of allowing convenient monitoring of cell physiological processes *in vivo* when the cells are implanted into a non-human animal. "Read-out" or information from the reporter cells or system may be in the form of qualitative or quantitative data and may involve invasive or non-invasive procedures in order to ascertain this data. Accordingly, one method of the present invention conveniently provides an animal model wherein multiple measurements may be made over a protracted period of time.

Preferably, the method of the invention further includes allowing the xenograft to proliferate as a xenograft tumour.

Preferably, the reporter cells/system may be introduced into an animal host either as individual cells suspended in suitable medium or as tissue fragments. The reporter cells/system may grow in the host animal either systemically, or as a xenograft at the site of implantation, possibly but not necessarily as a tumour with or without metastatic tumours at secondary sites.

Preferably, the host animal is immuno-suppressed by means of administration of appropriate immuno-suppressant agents or is of an immuno-compromised strain, for example and without limitation SCID. Alternatively, the reporter system may be grown in an immunologically intact animal where the reporter cells are syngeneic with the host animal.

Preferably, the reporter cells/system is/are genetically engineered to express a transgene or multiple transgenes. The reporter cells/system may be already expressing the transgene(s) at the time of implantation or may be transfected *in vivo* with a transgene in a specifically targeted manner, for example and without limitation, by means of a viral vector. Accordingly, it will be understood that the method of the present invention conveniently allows for transfection of cells prior to implantation or after implantation of the cells into the host animal.

Preferably, the reporter cell/system transgenes may comprise elements that allow measurement of relevant biochemical parameters in response to changes in cell physiology occurring during reporter cell proliferation or brought about by toxicological or pharmacological effects of administered compounds or biological substances.

Preferably, cell physiological processes that may be monitored by means of a suitable reporter molecules or transgenes include, for example and without limitation:

a) Parameters of xenograft growth or differentiation or death, such as for instance reporter cell numbers, cell cycle modulation or mitotic fraction, cell

differentiation, angiogenesis, hypoxia, cell death or lysis (for instance by apoptosis, necrosis);

b) Mechanisms of toxicity, such as for instance oxidative stress, DNA damage, mitochondrial function, membrane perturbation, GSH depletion, receptor-mediated toxicity, enzyme inhibition, cofactor availability, pH or osmotic change, perturbation of calcium homeostasis, cell differentiation, protein turnover, ubiquitination, protein misfolding;

c) Mechanisms of drug action, such as for instance effects on intracellular signalling pathways, receptor interactions, effects on gene transcription, translation or protein stability, hormone or growth factor receptor modulation; peroxisome proliferator-activated receptor modulation, intracellular signal transduction pathways such as for instance MAP kinase or phosphatase signalling, p53 signalling, ras signalling;

d) Induction of drug resistance mechanisms, drug delivery or drug bystander effects.

Reporter cells may preferably be genetically engineered to facilitate determination of the above processes through incorporation of at least one transgene whose expression products permit convenient determination of relevant parameters.

Suitable transgenes preferably comprise a naturally occurring or artificial promoter sequence driving expression of a gene resulting in production of a reporter or protein.

Preferably, the reporter expression products are detectable transcriptionally or post-transcriptionally.

In one embodiment of the invention (transcriptional reporting), the ability of the promoter to drive gene transcription is dependent either positively or negatively on the relevant parameters so that direct sensing of the gene products provides a read out of the relevant parameters.

In another embodiment of the invention (post-transcriptional reporting), the promoter is constitutively active or inducible by factors independent of the parameters to be determined, but the gene products have effects on or are affected by processes within the reporter cell in a manner that facilitates readout of the relevant parameters. Examples of such a method of obtaining read out include, for instance: a gene transcript or protein whose stability is positively or negatively dependent on the relevant parameters; a protein whose post-translational modification state, for instance its degree of phosphorylation, or whose subcellular localization or whose secretion from the expressing cell is dependent on the relevant parameters, or a protein with enzymatic activity catalysing modifications of either endogenous gene transcripts or proteins or products of other transgenes in the same cell such that those modifications provide a measurable read out.

It is envisaged that in the embodiment using transcriptional reporting, it could be mediated, for example, through suitable gene promoters, for example and without limitation the vascular endothelial growth factor (VEGF) promoter to detect hypoxia; the inducible nitric oxide synthetase (iNOS) promoter or the haemoxygenase-1 (HO-1) promoter or the cyclo-oxygenase-2 (COX-2) promoter to detect oxidative stress; the tissue transglutaminase promoter or the Peg3/pwl promoter to detect apoptosis, the 14-3-3 protein promoter or the GADD153 promoter to detect DNA damage. It will be appreciated that the foregoing list of suitable gene promoters is not intended to be limiting in the method of the present invention. The list of promoters is neither exhaustive nor exclusive and the skilled artisan may select any promoter that is capable of detecting a cellular physiological parameter that it is desired to monitor or measure.

In the embodiment employing post-transcriptional reporting, it could be effected through for example generation of a protein that can effect protein modifications, for example as a consequence of protease activity that result in translocation of a cytoplasmic protein to the nucleus or from membrane-bound form to secreted form or through protein cleavage that could for instance result in activation of a proenzyme or

transcription factor or deactivation of an active enzyme or transcription factor or in secretion into the blood or excretion into urine (e.g. Alanine aminotransferase). Post-transcriptional reporting could also involve, for instance, production of a protein or RNA that effects changes in the stabilisation of a protein or mRNA.

Preferably, the reporter cells/system may comprise genetic elements to facilitate detection of responses to relevant cell physiological parameters or intracellular signalling pathway activation. For instance, products of transgene expression may be chosen to allow convenient non-invasive assays in excreted body products, for instance in urine (for instance, human chorionic gonadotrophin, hCG), faeces, breath or saliva. Alternatively, products of transgene expression may be chosen to allow assay by non-invasive procedures, for instance by bioluminescence measurement, by blood pressure measurement, by transcutaneous oxygen tension measurement, by nuclear magnetic resonance measurement or by positron emission tomographic measurement of, for instance, glucose utilisation. Alternatively, products of transgene expression may be chosen to allow convenient invasive assays, for instance in blood (for instance secreted alkaline phosphatase, SEAP) or in xenograft tissue (for instance β-galactosidase or by "real-time" PCR of RNA from cells).

Transgene reporter products that are measured in blood, tissues or body products may preferably be assayed by, for instance, by immunoassay (for instance radioimmunoassay or enzyme-linked immunoassay, ELISA) or by enzymatic assay, or by colorimetric assay or by chromatographic assay (for instance HPLC) or by mass spectrometric assay or by nuclear magnetic resonance spectroscopy.

In another embodiment of the invention the reporter cells/system may incorporate multiple transgenes that could, for example, permit multiple forms of "read-out" of individual parameters from invasive and non-invasive intervention or simultaneous measurement of multiple parameters of interest, or to control for measured parameters being secondary to other parameters for example, cell proliferation that is secondary to angiogenesis.

Alternatively, reporter protein products of transgene expression under the control of different promoters may be distinguished by immunoassay by, for instance, incorporating into coding sequences of the transgene, coding sequences for clearly distinguishable epitope tags.

Particular advantages of the method of the present invention as described in step (iii) of the method is in providing methods of:

a) Making accurate measurement of reporter cell proliferation, particularly during xenograft growth or differentiation or death or in response to treatments;

b) Determining the mechanism of differentiation or death where reporter cell differentiation or death occurs;

c) Monitoring processes in secondary metastatic tumours to establish whether these differ in their responses from the primary reporter cell xenograft;

d) Making non-invasive measurements of parameters related to biochemical processes in the reporter cells;

e) Identifying drug-resistant cell populations, for instance arising from differential toxicity of a drug to dividing as compared to non-dividing cells or to hypoxic as opposed to normoxic cells;

f) Determining the effects of genetic background on tumour cell growth or on response to treatments, for instance in cells expressing and not expressing p53;

g) Making dynamic measurements using reporters of short half lives or that are excreted; and

h) Determining or confirming the targets of drug action *in vivo*; and

i) Measuring drug bystander effects; and identifying promoter elements involved in gene regulation; and

j) Determining intracellular drug concentrations and thereby those cells that take up a drug.

According to a further aspect of the invention there is provided a product comprising a genetically modified or engineered cell, the modification or engineering of the cell being such that the cell comprises at least one reporter molecule or reporter gene.

Preferably, the product further comprises any one or more of the features hereinbefore described.

According to a yet further aspect of the invention there is provided use of the method or product of the present invention in any one or more of the following examples:

(a) measuring reporter cell proliferation, particularly but not exclusively during xenograft growth or differentiation or death or in response to treatments;

(b) determining the mechanism of differentiation or death where reporter cell differentiation or death occurs;

(c) monitoring processes in secondary metastatic tumours where these may differ in their responses from the primary reporter cell xenograft;

(d) making non-invasive measurements of parameters related to biochemical processes in the reporter cell/system;

(e) identifying drug-resistant cell populations, for example arising from differential toxicity of a drug to dividing as compared to non-dividing cells or to hypoxic as opposed to normoxic cells;

(f) determining the effects of genetic background on tumour cell growth or on response to treatments, for instance in cells expressing and not expressing p53;

(g) making dynamic measurements using reporter molecules or genes of short half lives or that are excreted;

(h) determining or confirming the targets of drug action *in vivo*;

(i) measuring drug bystander effects; and identifying promoter elements involved in gene regulation;

(j) determining intracellular drug concentrations and thereby those cells that take up a drug; and

(k) determining or confirming the targets of drug action *in vivo*.

According to a yet further aspect of the present invention there is provided a kit comprising at least one reporter cell/system as hereinbefore described and optionally a set of instructions therefore. It is envisaged that the kit of the present invention may be supplied as a suspension of reporter cells.

Claims

1. A method of simulating progression of a xenograft in a non-human host animal comprising:

(i) genetically modifying or engineering a cell before or after implantation into an animal so as to incorporate at least one reporter molecule and/or reporter gene and/or reporter agent into said cell;

(ii) implanting said modified cell into said host animal and allowing a xenograft to grow for a sufficient period of time; and

(iii) measuring at least one parameter of a selected biochemical/ physiological response associated with the reporter molecule or reporter gene.

2. A method according to claim 1 wherein there is a plurality of genetically modified or engineered cells which are human or non-human in origin.

3. A method according to either preceding claim wherein the cell is a primary isolate derived from normal tissue or a tumour or is an immortalised or established cell line.

4. A method according to any preceding claim wherein the reporter molecule is selected from the group comprising a radionuclide, enzyme, enzyme substrate, fluorescent, chemiluminescent or chromogenic agent.

5. A method according to any preceding claim wherein the reporter gene is selected from those genes encoding proteins chloramphenicol, acetyltransferase, β–galactosidase, β–glucuronidase, luciferase, beta-galactosidase or green fluorescent protein, secreted alkaline phosphatase (SEAP), major urinary protein (MUP) or human chorionic gonadotrophin (hCG).

6. A method according to any previous claim where the reporter agent is a protease or kinase or where the reporter is a protein or RNA effecting changes in protein or mRNA stabilisation.

7. A method according to any preceding claim wherein the host animal is a rodent.

8. A method according to claim 7 wherein the rodent is a mouse or rat.

9. A method according to either claim 7 or 8 wherein the rodent is a wild type or genetically engineered mouse or rat having a specifically selected genetic background.

10. A method according to any preceding claim wherein the host animal has more than one different population of reporter cells/system implanted therein.

11. A method according to any preceding claim wherein the step comprising measuring at least one parameter of a selected biochemical/ physiological response associated with the reporter molecule or reporter gene or reporter agent a qualitative or quantitative measurement and may involve invasive or non-invasive procedures in order to ascertain such data.

12. A method according to any preceding claim wherein the xenograft is allowed to proliferate as a xenograft tumour with or without metastatic tumours at secondary sites.

13. A method according to any preceding claim wherein the implanted modified cells are introduced into the host animal either as individual cells suspended in suitable medium or as tumour fragments.

14. A method according to any preceding claim wherein the implanted modified cells are allowed to grow in the host animal either systemically or as a xenograft at the site of implantation.

15. A method according to any preceding claim wherein the host animal is either immunosuppressed by means of administration of appropriate immunosuppressant agents or is of an immunocompromised strain or is immunologically intact and wherein the implanted modified cells are syngeneic with the host animal.

16. A method according to any preceding claim wherein the reporter cell/system is genetically engineered to express a transgene or multiple transgenes.

17. A method according to any preceding claim wherein the reporter cell/system expresses the reporter gene(s) or agent(s) at the time of implantation or is transfected *in vivo* with the reporter gene or agent in a specifically targeted manner.

18. A method according to any preceding claim wherein the reporter gene(s) or agent(s) comprise at least one element that allow measurement of a biochemical parameter in response to either changes in cell physiology occurring during reporter cell/system proliferation or as a result of toxicological or pharmacological effects of an administered xenobiotic, compound or biological substance.

19. A method according to any preceding claim wherein the step of measuring at least one parameter of a selected biochemical/ physiological response associated with the reporter molecule or reporter gene or reporter agent comprises measuring or monitoring any one or more of the following parameters:

(a) reporter cell numbers, cell cycle modulation or mitotic fraction, cell differentiation, angiogenesis, hypoxia, cell death by necrosis, cell lysis or apoptosis;

(b) oxidative stress, DNA damage, mitochondrial function, membrane perturbation, GSH depletion, receptor-mediated toxicity, enzyme inhibition, cofactor

availability, pH or osmotic change, perturbation of calcium homeostasis, cell differentiation, protein turnover, ubiquitination or protein misfolding;

(c) effects on intracellular signalling pathways, receptor interactions, effects on gene transcription, translation or protein stability, hormone or growth factor receptor modulation, peroxisome proliferator-activated receptor modulation, intracellular signal transduction pathways, MAP kinase or phosphatase signalling, p53 signalling or ras signalling; and

(d) induction of drug resistance mechanisms, drug delivery or drug bystander effects.

20. A method according to any preceding claim wherein the reporter gene comprises a naturally occurring or artificial promoter sequence driving expression of a gene resulting in production of a reporter/protein.

21. A method according to claim 20 wherein the promoter is constitutively active or is inducible

22. A method according to any preceding claim wherein the reporter gene expression product(s) is/are reportable transcriptionally or post-transcriptionally.

23. A method according to claim 22 wherein transcriptional reporting is mediated by any one of the gene promoters selected from a group comprising, vascular endothelial growth factor (VEGF), nitric oxide synthetase (iNOS) promoter, haemoxygenase-I (HO-1) promoter, cyclo-oxygenase-2 (COX-2) promoter, transglutaminase promoter, Peg3/pwl promoter, 14-3-3 protein promoter or a GADD153 promoter.

24. A method according to claim 22 wherein post-transcriptional reporting is mediated through generation of a protein that can effect protein modifications, for example as a consequence of protease activity that result in translocation of a cytoplasmic protein to the nucleus or from membrane-bound form to secreted form or

through protein cleavage or activation of a proenzyme or transcription factor or deactivation of an active enzyme or transcription factor or in secretion into the blood or excretion into urine.

25. A method according to claim 22 wherein post-transcriptional reporting is mediated through production of a protein or RNA that effects changes in the stabilisation of a protein or mRNA.

26. A method according to claim 22 wherein post-transcriptional reporting is mediated through production of a protein which on death or lysis of the cell expressing it, is secreted or excreted, for instance alanine aminotransferase.

27. A method according to any preceding claim wherein measuring of at least one parameter of a selected biochemical/ physiological response associated with the reporter molecule or reporter gene or reporter agent is by means of either a non-invasive or an invasive assay wherein:

(i) the non-invasive assay is in excreted body products, or by bioluminescence measurement, or by blood pressure measurement, or by transcutaneous oxygen tension measurement, or by nuclear magnetic resonance measurement or by positron emission tomographic measurement; or

(ii) an invasive assay for blood or xenograft reporter products.

28. A product produced by the method of claim 1 and comprising a genetically modified or engineered cell, the modification or engineering of the cell being such that the cell comprises at least one reporter molecule or reporter gene.

29. A product according to claim 28 further including any one or more of the features recited in claims 2 to 27.

30. Use of the method of claim 1 or product of claim 28 in any one or more of the following situations:

(a) measuring reporter cell proliferation, particularly but not exclusively during xenograft growth or differentiation or death or in response to treatments;

(b) determining the mechanism of differentiation or death where reporter cell differentiation or death occurs;

(c) monitoring processes in secondary metastatic tumours where these may differ in their responses from the primary reporter cell xenograft;

(d) making non-invasive measurements of parameters related to biochemical processes in the reporter cell/system;

(e) identifying drug-resistant cell populations, for example arising from differential toxicity of a drug to dividing as compared to non-dividing cells or to hypoxic as opposed to normoxic cells;

(f) determining the effects of genetic background on tumour cell growth or on response to treatments, for instance in cells expressing and not expressing p53;

(g) making dynamic measurements using reporter molecules or genes of short half lives or that are excreted; and

(h) determining or confirming the targets of drug action *in vivo*; and

(i) measuring drug bystander effects; and identifying promoter elements involved in gene regulation; and

(j) determining intracellular drug concentrations and thereby those cells that take up a drug; and

(k) determining or confirming the targets of drug action *in vivo*.

31. A kit comprising a product with at least one reporter cell/system as defined in either claim 28 or 29 and optionally a set of instructions therefore.

32. A kit according to claim 31 wherein the product is supplied as a suspension of reporter cells.